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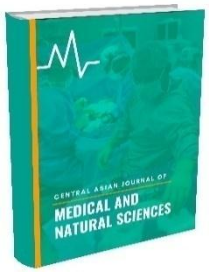

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Gout Therapy With Reduced Kidney Function

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Abstract: Gout is often combined with kidney disease. The pathology itself and concomitant hyperuricemia are considered as independent nephrotoxic factors. Urate-reducing therapy of gout can level the pathogenic effect of uric acid, preventing the development and progression of chronic kidney disease. However, in patients with reduced kidney function, its choice should be more careful. It is important to select not only the optimal urate-reducing drug, but also its dosing regimen. In this population, it is also difficult to set treatment goals and methods to evaluate its effectiveness. Xanthine oxidase inhibitors appear to be the most promising in the presence of renal pathology.

Key words: gout, kidney disease, febuxostat, allopurinol.

The association between gout and renal disease has long been established and is generally accepted. Large studies in recent years have demonstrated the role of gout and hyperuricemia as independent risk factors for chronic kidney disease (CKD) [1-5]. At the same time, it is known that as renal function decreases, urinary excretion of uric acid (UA) decreases, contributing to hyperuricaemia and thus increasing the likelihood of gout, as well as preventing the achievement of target levels of UA when the disease has already developed.

The paradigm of gout is considered to be inflammation arising at the sites of deposition of sodium salt UA crystals and manifested by acute attacks of arthritis [2]. Crystal formation is only possible under conditions of hyperuricemia. When the level of UA is normalized, the crystals dissolve [7], which allows to consider gout as a potentially treatable disease [8].

The mechanism of microcrystalline inflammation in gout is universal regardless of its localization, including the deposition of UA crystals in the kidneys [3-6]. The clinical manifestations and consequences of acute attacks of arthritis and chronic inflammation in gout are directly related to the stimulation by sodium monourate crystals of the NLP3 inflammasome with subsequent secretion by caspase 1 activation and release of proinflammatory cytokines, primarily interleukin (IL) 1β, which is the trigger of the inflammatory cascade [5, 6]. This mechanism is continuous, persistent, and leads to chronic subclinical inflammation persisting in joints and other sites of sodium monourate crystal

deposition during remission [7]. Relapses of acute attacks of gouty arthritis, characterized by severe pain, local hyperthermia, often fever, and unpredictability, are indicative of the presence of crystals in the body [6-8].

In dissolved form, UA has sufficient proinflammatory potential to induce an inflammatory process in the kidneys [9].

MC has autocrine, paracrine and endocrine effects. High intracellular concentration of urate in addition to the transcription factor NF-kB stimulates mitogen-activated protein kinase signaling pathways and growth factors, vasoconstrictors (angiotensin II, thromboxane, endothelin), chemokines, and promotes mitochondrial dysfunction [8]. Hyperuricemia affects endothelial cell function by inhibiting their proliferation and migration, reducing nitric oxide bioavailability in endothelium [9].

A similar mechanism of inflammation in gout leads to the development of acute and chronic renal disease with damage to renal tubules and the formation of tubulointerstitial fibrosis [9, 14].

A recent meta-analysis involving eight studies showed that 24% (95% confidence interval (CI) 19-28) of patients with gout develop stage III or more CKD [24]. According to the results of a retrospective cohort study by A.G. Stack et al. involving 68,897 patients with gout and 554,964 controls, CKD in gout developed significantly more frequently, 8.54 per 1000 patient-years (95% CI 8.26-8.83) versus 4.08 (95% CI 4.00-4.16) [2].

It should be noted that in the general population the prevalence of CKD is significant and continuously increases with age. According to a global meta-analysis, which included about a hundred studies, CKD affects from 11 to 13% of the population, the most common being stage III CKD - up to 7.6% (more than half of all patients with CKD). At the same time, women suffer more often than men - 14.6 vs. 12.8%. The prevalence of CKD increases with age, but the stage ratio does not change [11]. The incidence of CKD in patients with gout is much higher. It can reach 20% [14]. At the same time, the risk of progression of CKD to the terminal stage increases significantly [1, 6].

As noted previously, the likelihood of developing gout in CKD is increased by decreased MC excretion. The prevalence of gout in a cohort of patients with a calculated glomerular filtration rate (GFR) $\geq$ 60 mL/min/1.73 m ^{2}is 16%, and with a calculated GFR < 30 mL/min/1.73 m ^{2}is 35.6%, which is almost twice as high [18]. E. Mohammed et al. found that the incidence of gout increased with increasing stage of CKD, from 7.5% in stage I and II CKD to 22.8% in stage IV and V CKD ($p < 0.005$) [9].

Chronic kidney disease has a significant impact on the management of patients with gout. Limitations in drug selection and dose selection, as well as the potential impact of such therapy on the progression and prognosis of CKD, must be considered (10,11). Treatment of gout involves the use of drugs for the management of acute attacks(non-steroidal anti-inflammatory drugs,colchicine, glucocorticosteroids and IL-1 inhibitors)and urate-lowering drugs to maintain serum levels of UA, in which attacks are unlikely to occur and UA crystal deposits gradually dissolve [8]. The maintenance of the target level should be lifelong. Treatment with a regimen of urate-lowering drugs with medication won't be enough.

What are the specific features of prescribing urate-reducing therapy in patients with gout in CKD?

Currently, urate-lowering therapy is represented by xanthine oxidase inhibitors, uricosurics and pegylated urease preparations [12]. The most commonly used xanthine oxidase inhibitors are allopurinol and febuxostat, which reduce UA levels by inhibiting its formation.

Uricosuric drugs such as probenecid, benzbromaron, sulfinpyrazone and lezinurad affect reabsorption of MC and increase its excretion by the kidneys. However, the use of most uricosuric drugs is contraindicated or ineffective if renal function is significantly reduced - FSR

< 30 ml/min/1.73 m^2. Lesinurad should not be used if FFR is less than 45 mL/min/1.73 m^2. Only benzbromarone has a FSR limitation of 20 mL/min/1.73 m^2[10]. However, neither lezinurad nor benzbromaron are not registered in the Russian Federation. Drugs of this class are usually prescribed in combination with xanthine oxidase inhibitors when their effectiveness is insufficient.

Preparations of pegylated uricase (peglotikase) convert UA to allantoin, dramatically reducing its blood levels. Peglotycases, which can be used in patients with CKD regardless of its stage and which do not reduce FSR [13], are not registered for use in all countries and also have some limitations [14]. The feasibility of their use is limited due to their high cost and poor tolerability.

Thus, xanthine oxidase inhibitors remain the main drugs for the treatment of gout. They can have a positive effect on renal function by reducing serum UA levels (15, 16). The potential nephroprotective effect may also be associated with the reduction of oxidative stress, inflammation, prevention of the development of glomerular hypertension and arteriolar wall thickening [12].

According to the meta-analysis conducted by A. Pisano et al. in the group of xanthine oxidase inhibitors, allopurinol is recognized as a first-line therapy. It has been used for the treatment of gout for more than 50 years. In the body allopurinol converts into an active metabolite - oxypurinol, which competitively inhibits xanthine oxidase, resulting in reduction of xanthine and hypoxanthine levels, as well as UA production. Oxipurinol is excreted by the kidneys mainly unchanged. In normal function, the elimination half-life is up to 30 hours. In severe CKD, the elimination time decreases in parallel with a decrease in GFR and may increase for up to one week (10).

The maximum allopurinol dose may be 900 mg/day with preserved renal function, but this is not safe if creatinine clearance is markedly reduced (13). The main risks of allopurinol administration are associated with hypersensitivity syndrome and severe skin reactions. This occurs more frequently at a starting dose of 400 mg/day and more than at a dose of 100 mg/day. In the first case, the risk increases 23-fold [14].

In patients with CKD, allopurinol administration is associated with a higher incidence of hypersensitivity reactions, especially if the dose is not adjusted according to FSR at therapy initiation (43). A number of studies have demonstrated that even standard allopurinol doses (200- 400 mg/day) in patients with CKD increase the risk of severe skin reactions. These are due to the accumulation of oxypurinol and are most common in the first 60 days of treatment (13).

Thus, the starting dose of allopurinol should not exceed 100 mg/day, its further escalation is carried out gradually (50-100 mg/day every two to four weeks). The dose should be limited according to creatinine clearance values (table). Allopurinol doses are presented based on an average daily dose (300 mg/day), the maximum tolerated dose is 800-900 mg/day (depending on national guidelines).

It is important to emphasise that an allopurinol dose based on creatinine clearance will be safe for patients, but will often not address the primary objective of achieving target UA levels. Thus, if this dosing strategy is followed, the likelihood of achieving the target UA level is less than 50% (15). In allopurinol prescribing in patients with baseline reduced GFR, even in less than stage III CKD, due to dose limitation (often in the range of 100-200 mg/day), the UA level is not reduced sufficiently, the target level is achieved by less than 30% [14].

In patients with CKD at high risk of severe skin reactions, failure to achieve the target UA level against the background of maximum tolerated doses of allopurinol, it is necessary to prescribe other urate-lowering drugs, in particular febuxostat (figure).

Febuxostat, firstly, more often allows to reach target UA level, including in most patients with allopurinol ineffectiveness, especially in the presence of reduced renal function [16], secondly, has an advantage over allopurinol in relation to dynamics of FSR in conditions of renal insufficiency [17].

Possible reasons for the high efficacy of febuxostat in patients with CKD include the predominance of metabolism in the liver (up to 70%), i.e. no dependence on creatinine clearance, and the inhibition of two isoforms of xanthine oxidase [16].

Febuxostat can be used in patients with gout and CKD in doses of 80 and 120 mg/day without correction depending on FSR. There is also evidence of success in this population with febuxostat at a dose of 240 mg/day, which exceeds the maximum recommended daily dose. In a study by H.R. Schumacher et al. study, the patients receiving febuxostat in any dose (80, 120 or

240 mg/day) significantly more often reached the target UA level than those receiving allopurinol in doses of 100 or 300 mg/day (corrected according to renal function) ($p < 0.05$) [22].

The results of a double-blind, randomized CONFIRM trial with more than 2,000 patients with gout have shown that febuxostat 80 mg/day reached the target UA level in 71.6% of patients, whereas allopurinol prescribed at a dose of 300 or 200 mg/day at a calculated GFR of 30 to 89 ml/min/1.73 m ^{2}had only 42.3% [20].

According to X. Zhang et al., in patients with gout and CKD who received febuxostat, MC level was significantly lower than that in those who used allopurinol ($p = 0.02$). At the same time, the risk of decreasing FFR by more than 10% from baseline was significantly lower - 17.9 vs 34.1% ($p = 0.025$) [23].

In a cohort study conducted by H.W. Chou et al., 874 patients were divided into three groups: the first (n = 337) received allopurinol, the second (n = 138) - febuxostat, the third (n = 399) - benzbromaron [17]. The study showed that febuxostat was more effective in reducing MC levels than allopurinol and benzbromaron. In addition, febuxostat and benzbromaron were associated with a lower risk of terminal renal failure than allopurinol.

A meta-analysis of 11 studies involving 1,317 patients showed that estimated GFR was significantly higher in patients with stage III and IV CKD treated with febuxostat [20]. In the EXCEL study, febuxostat compared with allopurinol resulted in a more persistent reduction in MC, which in turn was associated with improved renal function ($p = 0.001$) [19].

In 2019, X. Liu et al. published the results of a single-center prospective study involving patients with stage III to stage V CKD [21]. 112 patients received therapy with febuxostat, 96 with allopurinol. Achievement of MC level < 360 mmol/l was chosen as a criterion of treatment efficacy. Renal function was also evaluated. The target UA level after six months was achieved by 96.4% in the febuxostat group and 37.5% in the allopurinol group. Estimated GFR in the febuxostat group increased from 28.45 to 30.65 ml/min/1.73 m ^{2}, in the allopurinol group decreased from 28.06 to 24.39 ml/min/1.73 m ^{2}. Linear regression analysis demonstrated that a decrease in uric acid level was significantly associated with an increase in estimated GFR and a decrease in proteinuria.

No dose adjustment of febuxostat is required even in patients with severe renal impairment (stage III or higher CKD). At the start of therapy, 80 mg/day is the optimal dose. In case of underachievement of target uric acid level on average after two weeks it is reasonable to increase it to maximum - 120 mg/day. A daily dose of febuxostat, as well as a daily dose of allopurinol, is administered simultaneously.

Thus, despite some difficulties in selecting urate-lowering therapy for patients with gout and restricted renal function, achieving target uric acid levels and controlling the disease is possible in most cases. The key to the success of therapy is adherence to prescribing guidelines.

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